REMARKS

Claims 1-77 and 113-140 are pending. Claims 27-35, 48-77 and 113-140 are withdrawn as directed to nonelected subject matter. Claims 6, 8, 10, 12-26, 42-44, 46 and 47 read on the elected species and were examined.

35 U.S.C. § 103 Rejections

Reconsideration is respectfully requested of the rejection of claims 6, 8, 10, 12-26, 42-44, 46, and 47 for being unpatentable over Gregg et al. (U.S. Patent No. 5,264,105) in view of Saini et al. (U.S. Patent No. 5,521,101), and further in view of Yamamoto et al. (U.S. Patent Application Publication No. 2002/0127440), and still further in view of Wilson (U.S. Patent No. 5,211,984). Gregg is described as teaching a

> bioanode comprising (a) an electron conductor; (b) at least one enzyme capable of reacting with an oxidized form of an electron mediator and a fuel fluid to produce an oxidized form of the fuel fluid and a reduced form of the electron mediator, the reduced form of the electron mediator being capable of releasing electrons to the electron conductor; and (c) an enzyme immobilization material comprising the electron mediator, the enzyme immobilization material being capable of immobilizing and stabilizing the enzyme, the material being permeable to the fuel fluid.[1]

Saini et al. is relied upon by the Office as disclosing a "biocathode having a gold microband (electron conductor), polyphenol oxidase, quinone (electron mediator), and a polymeric material (enzyme immobilization material)" and "the polymeric material is Nafion (perfluoro sulfonic acid-PTFE copolymer)."[2] Yamamoto is relied upon as teaching an electrode made of carbon paper. The Office asserts that Wilson teaches a tertbutyl ammonium modified perfluorosulfonic acid and the "modification yields robustness of the material and eliminates acid groups by the bulky ammonium sidegroups. The Office action further states that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Yamamoto's carbon paper for Gregg's glassy carbon because they are both carbon and conductive material."[3] Also, the Office action states that "it would have been obvious to one of ordinary skill in the art at the time the invention was made modify Gregg's Nafion with tertbutyl ammonium ion and

[1] See Office action dated October 10, 2006 at page 3.
[2] See Office action dated October 10, 2006 at page 3.
[3] See Office action dated October 10, 2006 at page 3.

enzyme-Nafion compositions, as taught by Wilson and Saini taken collectively, for the benefit of eliminating acid groups and increasing the robustness of the immobilizing material."[4] Therefore, it is the Office's position that it would have been obvious to (1) substitute Yamamoto's carbon paper for Gregg's glassy carbon electrode; and (2) modify Gregg's Nafion with tert-butyl ammonium as suggested by Wilson for eliminating acid groups and increasing the robustness of the enzyme immobilization material.

In this case, claim 6 requires the elements of (1) an electron conductor, (2) an enzyme capable of reacting with an oxidized form of an electron mediator and a fuel fluid to produce an oxidized form of the fuel fluid and a reduced form of the electron mediator, (3) the reduced form of the electron mediator being capable of releasing electrons to the electron conductor, (4) an enzyme immobilization material being capable of immobilizing and stabilizing the enzyme, (5) the enzyme immobilization material being permeable to the fuel fluid, and (6) the enzyme immobilization material comprising the electron mediator. The terms immobilizing and stabilizing are interpreted in light of the specification. Thus, an immobilized enzyme is interpreted as an enzyme that is physically confined to a certain region of the enzyme immobilization material while retaining its catalytic activity[5] and a stabilized enzyme is an enzyme that retains at least about 75% of its initial catalytic activity for at least about 30 days to about 365 days.[6]

Gregg et al.

Gregg et al. generally disclose enzyme electrodes that contain a three-dimensional redox polymer network that has bound redox enzymes for use in amperometric biosensors. Although Gregg et al. describe enzymes that are immobilized within redox polymers, the reference is silent on the stability of these enzymes within the electrodes. Further, a skilled person would have expected the enzyme to denature in a shorter time span than the enzymes immobilized in enzyme immobilization materials of the bioanodes of the instant claims because publications and presentations describing this work disclosed that the enzymes within the electrodes described by Gregg et al. retained at least about 75% of their initial catalytic activity upon continuous use for

[4] See Office action dated October 10, 2006 at page 3.
[5] See specification at page 7, paragraph 33.
[6] See specification at pages 6-7, paragraph 29.

about 3 days.[7] Therefore, applicants respectfully submit that Gregg et al. do not describe or suggest an enzyme immobilization material capable of stabilizing the enzyme.

Additionally, claim 12 depends on claim 6 and further requires a modified perfluoro sulfonic acid-PTFE copolymer. While Gregg does disclose a perfluoro sulfonic acid-PTFE copolymer, it is not an enzyme immobilization material as claimed and it is not a modified perfluoro sulfonic acid-PTFE copolymer. The perfluoro sulfonic acid-PTFE copolymer (Nafion®) is used as a film to prevent diffusion of macromolecules into the assayed solution. Thus, Gregg does not disclose, nor contemplate an enzyme immobilization material comprising either a perfluoro sulfonic acid-PTFE copolymer (Nafion®) or a modified perfluoro sulfonic acid-PTFE copolymer.

Saini et al.

Saini et al. generally disclose sensors for monitoring analytes in the gaseous phase. Saini et al. is relied upon by the Office as disclosing a "biocathode having a gold microband (electron conductor), polyphenol oxidase, quinone (electron mediator), and a polymeric material (enzyme immobilization material)" and "the polymeric material is Nafion (perfluoro sulfonic acid-PTFE copolymer)."[8]

As described in more detail above, claim 6 requires an enzyme immobilization material that immobilizes and stabilizes the enzyme. The enzyme immobilization materials described by Saini et al. do not meet the enzyme stabilization requirement of claim 6. For example, when Nafion® was used to immobilize the enzyme, Saini et al. describe the results as follows:

> Enzyme-Nafion modified electrodes were only biocatalytically active for approximately 30 minutes. The enzyme was presumed to be inactivated by the acidic groups of the Nafion polymer and/or excessive dehydration.[9]

By way of further example, when ionically conducting gels of tetrabutylammonium toluene-4-sulfonate were used as the enzyme immobilization material, Saini et al. describes the enzyme as having limited stability since the "enzyme proved to be relatively stable for a number of hours within the gel matrix."[10] Thus, the enzymes immobilized at electrodes described by Saini et al.

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[7] See, for example, Non-Patent Literature Reference #1 of Supplemental IDS dated June 29, 2006, Chen et al., *J. Am. Chem. Soc.* **2001**, *123*, 8630-8631 (Figure 4 shows the current of the biofuel cell reaches 75% of the initial current after about 3 days (72 hours)).
[8] See Office action dated October 10, 2006 at page 3.
[9] U.S. Patent No. 5,521,101 at column 12, lines 14-17.
[10] U.S. Patent No. 5,521,101 at column 13, lines 38-39.

were stable for only a number of hours, whereas claim 6 and the claims that depend therefrom require the enzyme to retain at least about 75% of its initial catalytic activity for at least about 30 days. Thus, the Saini et al. disclosure does not disclose or suggest enzyme immobilization materials that meet the enzyme stability requirement of claim 6, and does not overcome the deficiencies of the Gregg et al. reference.

Further, as described in more detail above, claim 12 includes all the elements of claim 6 and further requires the enzyme immobilization material be a modified perfluoro sulfonic acid-PTFE copolymer. In contrast, Saini et al. disclose use of Nafion® (a perfluoro sulfonic acid-PTFE copolymer). Saini et al. do not disclose or suggest use of a modified perfluoro sulfonic acid-PTFE copolymer.

In particular, with the disclosure of Saini et al. that the enzyme immobilization materials provide enzymes retaining catalytic activity for only several hours, a person skilled in the art would not have been led to modify the electrodes of Gregg et al. to arrive at the claimed bioanodes. Due to this inferior enzyme stability data, the disclosure of Saini et al. alone or in combination with the Gregg et al. disclosure would have led one skilled in the art away from using Nafion® as an enzyme immobilization material and also would not have provided a reasonable expectation that electrodes containing Nafion® or modified Nafion® enzyme immobilization materials would have provided the enzyme stability required by the claimed bioanodes. Therefore, regardless of whether or not one skilled in the art would have modified Saini's electrode, one still would not have arrived at the claimed invention because the enzyme stability requirement would not have been met.

Further, neither Saini et al. nor Gregg et al. suggest use of a modified perfluoro sulfonic acid-PTFE copolymer as an enzyme immobilization material as required by claim 12. Gregg et al. did not disclose any immobilization materials generically or specifically that would have suggested using modified perfluoro sulfonic acid-PTFE copolymer as an enzyme immobilization material. Actually, the data presented in Saini et al. wherein the Nafion® enzyme immobilization material allows the enzyme to retain its catalytic activity for only 30 minutes would have led a person skilled in the art away from use of a Nafion polymer as an enzyme immobilization material.

Wilson

The Office further cited Wilson with regard to modified Nafion. The Office asserts that Wilson teaches a tertbutyl ammonium modified perfluorosulfonic acid and the "modification yields robustness of the material and eliminates acid groups by the bulky ammonium sidegroups. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made modify Gregg's Nafion with tertbutyl ammonium ion and enzyme-Nafion compositions, as taught by Wilson and Saini taken collectively, for the benefit of eliminating acid groups and increasing the robustness of the immobilizing material."[11]

Wilson generally discloses gas reaction fuel cells incorporating a thin catalyst layer between a solid polymer electrolyte membrane and a porous electrode backing. A platinum catalyst is used in the fuel cells. Wilson also teaches a thermoplastic form of a perfluorosulfonate ionomer that is obtained by ion-exchange of a hydrophobic cation, such as tetra-butyl ammonium hydroxide (TBAOH) with the proton form of the ionomer. The thermoplastic TBA^+ (tetrabutylammonium) form is made by adding an equal molar amount of TBAOH to perfluorosulfonate ionomer (Nafion®) that is mixed with a catalyst in solution. By using the TBA^+ form of Nafion®, the membrane assembly can be hot pressed at a higher temperature and because it is thermoplastic, the TBA^+ form of Nafion® deforms onto the membrane and provides better adhesion and continuity. The Office states "[t]he modification yields robustness of the material and eliminates acid groups by the bulky ammonium side groups."[12] However, the robustness necessary for the solid polymer electrolyte membranes of Wilson is the ability to be hot pressed at a higher temperature and to deform at such a temperature to provide a more adherent and continuous catalyst layer. These properties are not generally advantageous for an enzyme immobilization material because when the enzyme is heated significantly above physiological temperature, it denatures much more quickly.

Further, upon reading the disclosure of Wilson, a person skilled in the art would not have known whether the modified perfluorosulfonate ionomers described would have the desired properties in terms of immobilizing (physically confining to a certain region) the enzyme. In fact, due to the relative pore sizes produced in a material prepared by Wilson's modification procedure, this procedure does not produce modified Nafion® membranes that immobilize and stabilize an enzyme. By way of example, applicant's specification teaches that for more stable

[11] See Office action dated October 10, 2006 at page 3.
[12] See id.

and reproducible modified Nafion® membranes, the excess salts must be removed from the casting solution to eliminate "complications from excess salt that may be trapped in the pore or may cause voids in the equilibrated membrane."[13] In contrast, the reaction of Nafion® with TBAOH as described in the Wilson reference does not include such a salt-extraction step. The modified Nafion® membranes produced by Wilson's method would consequently have pores that include the salts that would render the pores too large and irregular to provide an immobilized, stabilized enzyme. Also, for many enzymes, activity would be lost upon immobilization in a modified Nafion® membrane prepared by the procedure described by Wilson because without the salt-extraction step, the modified Nafion® membranes would still contain acid groups that would inactivate these enzymes. For these reasons, the procedure described in Wilson would not have produced enzyme immobilization materials that would meet the requirements of claim 6.

Moreover, the purpose of the modified Nafion® in the Wilson reference is to provide a continuous layer of a precious metal catalyst while the purpose of the enzyme immobilization material of the instant claims is to immobilize and stabilize the enzyme and provide an environment that is advantageous for retention of the enzyme's catalytic activity. Because the problems of providing a proper environment for a precious metal catalyst in a gas exchange fuel cell and of providing a proper environment for a biological catalyst in a biofuel cell are very different, the teachings of Wilson would not have led a person skilled in the art to modify Nafion® to arrive at the bioanodes of claims 6, 12, and 17-22. In fact, the teachings of Saini et al. that unmodified Nafion® immobilization materials provide enzymes that retain their catalytic activity for only 30 minutes would have led a person skilled in the art away from using Nafion® in any form as an enzyme immobilization material. Regardless of whether or not one skilled in the art would have been motivated to modify the Nafion®, one would not have expected the Nafion® modification to improve enzyme stability from being "relatively stable for hours" to at least 30 day stability.

Yamamoto et al.

The Office further asserts that Yamamoto teaches that "the electrode is made of carbon paper. Thus, it would have been obvious to one of ordinary skill in the art at the time the

[13] See specification at page 14, paragraph 45.

invention was made to substitute Yamamoto's carbon paper for Gregg's glassy carbon because they are both carbon and conductive material."[14]

Yamamoto et al. generally disclose polymer electrolyte fuel cells containing an anode and a cathode containing platinum wherein oxidation of hydrogen to water occurs at the anode and reduction of oxygen to water occurs at the cathode. The disclosure of Yamamoto et al. also describes a fuel supply path that includes a biochemical catalyst that generally produces hydrogen from an organic fuel. Regardless of whether one skilled in the art would have been motivated to make the modification advanced by the Office, Yamamoto et al. fail to address the deficiencies of Gregg et al., Saini et al. and Wilson with respect to the extent of stabilization of the enzyme by the enzyme immobilization material. Thus, a person of ordinary skill would not have been led from the combined teachings of Gregg et al., Saini et al., Wilson and Yamamoto et al. to develop the bioanodes of claim 16 nor would they have had a reasonable expectation from the references that the bioanodes would have the required enzyme stability.

Moreover, the Office is engaged in impermissible hindsight by focusing on isolated teachings in each individual reference rather than taking the cited references as a whole. When Gregg et al., Saini et al., Wilson and Yamamoto et al. are considered as a whole a skilled artisan would not have contemplated developing bioanodes containing enzymes having the required stability without the aid of applicant's disclosure. Thus, in sum, claims 6, 8, 10, 12-26, 42-44, 46, and 47 are patentable in view of the cited references.

Rejoinder

Pursuant to M.P.E.P. §821.04, Applicants also request rejoinder of withdrawn claims 27-35, 49-52, 60-62, 114, and 117-130 as they depend from claim 6 and therefore require all the limitations of claim 6.

Related Applications

Applicant also has related applications that are pending; these applications have U.S. Serial Nos. 10/931,147 and 10/598,951.

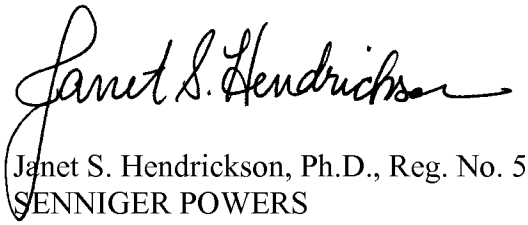
[14] See Office action dated October 10, 2006 at page 3.

CONCLUSION

Applicant submits that the present application is now in condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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